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REVIEWS

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HHV-6 in liver transplantation: A literature review

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Abstract

Human herpesvirus 6 (HHV-6A and HHV-6B) can cause primary infection or reactivate from latency in liver transplant recipients, which can result in a variety of clinical syndromes, including fever, hepatitis, encephalitis and higher rates of graft dysfunction as well as indirect effects including increased risks of mortality, CMV disease, hepatitis C progression and greater fibrosis scores. Although HHV-6 infection is currently diagnosed by quantifying viral DNA in plasma or blood, biopsy to demonstrate histopathological effects of HHV-6 remains the gold standard for diagnosis of end-organ disease. HHV-6 reactivation may be restricted to the infected organ with no evidence of active infection in the blood. HHV-6 infections in liver transplant patients are mostly asymptomatic, but clinically significant tissue-invasive infections have been treated successfully with ganciclovir, foscarnet or cidofovir. Inherited chromosomally integrated HHV-6 (ciHHV-6), in either the recipient or the donor organ, may create confusion about systemic HHV-6 infection. Recipients with inherited ciHHV-6 may have an increased risk of opportunistic infection and graft rejection. This article reviews the current scientific data on the clinical effects, risk factors, pathogenesis, diagnosis and treatment of HHV-6 infections in liver transplant recipients.

KEYWORDS
chromosomally integrated HHV-6 (CIHHV-6), human herpesvirus 6 (HHV-6), liver transplantation

1 | INTRODUCTION

Human herpesvirus 6 (HHV-6) is the common collective name for the two distinct viruses known as human herpesvirus 6A (HHV-6A) and human herpesvirus 6B (HHV-6B).[1] HHV-6A, HHV-6B and HHV-7 make up the *Roseolovirus* genus, aetiological agents of roseola, a common disease in infants. Like other herpesviruses, HHV-6 establishes life-long latency in human hosts and may reactivate under certain situations later in life. HHV-6 is a ubiquitous virus that typically causes primary infection in children, most commonly before the age of 2 years.[2] Since over 95% of humans are infected, the vast majority of active HHV-6 infections detected in adults are thought to be because of the reactivation of endogenous latent HHV-6. However, primary HHV-6 infection can still occur in seronegative adults.[3] Primary HHV-6 infection in children may manifest as non-specific fever, diarrhoea and rash (known as exanthema subitum or roseola infantum).[4] HHV-6 is the most common cause of hospital visits in infants with fever, accounting for 20% of all cases of acute fever in children between 6 and 12 months old.[2,5] The absence of HHV-6-specific antibodies during active viraemia is indicative of primary infection.

HHV-6 reactivation is often diagnosed by testing for the presence of viral DNA in plasma, whole blood or peripheral blood mononuclear cells (PBMCs). HHV-6 reactivation can also be identified by HHV-6 antigenaemia, demonstration of virus-specific proteins from tissue biopsies, or the detection of HHV-6 messenger RNA. Since latent HHV-6 DNA is ubiquitous and clinically insignificant viral reactivation occurs

Abbreviations: ALF, acute liver failure; CDV, cidofovir; ciHHV-6, chromosomally integrated HHV-6; CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; FISH, fluorescent in situ hybridization; GCV, ganciclovir; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-6+, HHV-6-positive; HHV-6-, HHV-6-negative; HSV, human simplex virus; IFA, immunofluorescent assay; IHC, immunohistochemistry; IL, interleukin; ISH, in situ hybridization; OKT3, muromonab-CD3; PBMC, peripheral blood mononuclear cell; qPCR, real-time quantitative PCR; RT-PCR, reverse transcriptase PCR; SOT, solid organ transplant; TNF, tumour necrosis factor; VGV, valganciclovir.

commonly in immunosuppressed patients, the interpretation of HHV-6 DNA in blood and/or liver tissue after liver transplantation is challenging. HHV-6 infections are mostly asymptomatic, although clinically significant HHV-6 infections in liver transplant patients may be understated since an infection may be active in the liver without remarkable DNA levels in the PBMCs or plasma. HHV-6A&B can infect hepatocytes and establish latency, where they can induce the release of cytokines that may cause hepatic cell injury.[6–8] HHV-6 infection can be treated with ganciclovir, foscarnet or cidofovir. We conducted a literature review to provide a state of the art evaluation of HHV-6 in liver transplantation, including its epidemiology, clinical effects, diagnosis and treatment.

Key points

- HHV-6 reactivation after liver transplantation is mostly asymptomatic but can be associated with fever, hepatitis and encephalitis.
- Tissue-invasive HHV-6 disease cannot be completely ruled out without a biopsy since infections can be localized in the tissue without remarkable DNA levels in blood. Quantitative assays are essential to distinguish active from latent HHV-6 DNA.
- When testing for the presence of HHV-6, ciHHV-6 in either donor or recipient must be considered.
- Symptomatic and tissue-invasive HHV-6 infections in liver transplant recipients can be successfully treated using ganciclovir, foscarnet or cidofovir.

2 | HHV-6 TRANSPLANT EPIDEMIOLOGY

HHV-6 is often reactivated from latency during periods of intense immunosuppression, although sporadic cases of HHV-6 reactivation have been reported even in the immunocompetent.[9–12] HHV-6A & B are increasingly recognized as pathogens that can cause primary infection or reactivate from latency in liver transplant recipients, resulting in a variety of adverse clinical syndromes including fever, hepatitis and encephalitis, as well as higher rates of HCV progression and CMV reactivation, graft failure and mortality. The virus found in liver transplants is almost always HHV-6B.[13–17] The frequency of HHV-6 reactivation after liver transplantation is approximately the same in plasma (33%) and PBMCs (34%) (Table 2). Reported reactivation rates vary and depend on whether or not patients were administered CMV prophylaxis that effectively covers HHV-6. In the studies summarized in Table 3, 50 (11%) of the 455 patients receiving CMV prophylaxis reactivated HHV-6 vs 167 (39%) of the 433 patients receiving acyclovir or no prophylaxis.

Unique to HHV-6 is the ability to integrate their viral genome into the human host chromosome. Known as inherited chromosomally integrated HHV-6 (ciHHV-6), it is naturally passed through the germ line in a Mendelian fashion.[18] The clinical consequences of ciHHV-6 in the immunocompromised host are actively debated.[19] Among liver transplant patients with ciHHV-6, 2% are reported to present with extremely high viral loads in whole blood (>5.5 $\log_{10}$ copies/mL), compared to 0.85% in control patients[20] indicating that almost 3% of liver transplants could be affected by ciHHV6 in either the donor or recipient. The ciHHV-6 prevalence in the Mayo Clinic liver study[21] was stated to be (1.3%) based on an arbitrary threshold of 1 million copies/mL. However, this threshold excluded a patient with over 5.5 $\log_{10}$ copies/mL who was likely ciHHV-6+, suggesting that the true prevalence was probably 1.6% or twice the rate found in healthy controls. It is now known that the integrated virus can activate[19] and may be stimulated by HDAC inhibitors and steroids.[22]

3 | CONDITIONS ASSOCIATED WITH HHV-6 IN LIVER TRANSPLANT PATIENTS

3.1 | Asymptomatic Infection

Many immunosuppressed transplant patients develop transient and asymptomatic HHV-6 infections demonstrated by low-level quantitative PCR DNA levels.[8,23] These transient reactivations do not require treatment.

3.2 | Fever

Patients with clinically significant HHV-6 infection after liver transplantation commonly present with unexplained fever.[8,24,25] Among adult transplant patients with HHV-6 plasma viraemia, five (29.4%) of 17 presented with unexplained fever at the time of reactivation.[8] Fever may be associated with skin rash,[25,26] myelosuppression[27] or elevated transaminases.[28–30]

3.3 | Hepatitis

HHV-6 has been implicated as cause of hepatitis in solid organ transplant (SOT) patients.[30,31] In liver transplant patients, HHV-6 reactivation is associated with elevated transaminases,[11,28–30] portal lymphocytic infiltration on liver biopsy[28,32] and acute rejection.[15] One case report described an HHV-6B infected liver transplant patient who developed donor-transmitted HHV-6A superinfection that manifested as syncytial giant cell hepatitis.[30]

A recent study found that HHV-6 DNA was detectable in 10 of 26 (38.5%) liver biopsy specimens diagnosed with graft acute hepatitis of undetermined origin.[31] In 4 (40%) of the 10 patients, confluent periportal necrosis was associated with high tissue HHV-6 viral load on liver biopsy. In contrast, periportal necrosis was absent in graft hepatitis not documented to be associated with HHV-6. Hence, the presence of confluent periportal necrosis with high intragraft viral load may indicate HHV-6-induced hepatitis. Notably, only 28.6% of patients with HHV-6-positive graft hepatitis had elevated levels of HHV-6 in the PBMCs associated with active infection. The authors concluded that in over two-thirds of cases, the reactivation of HHV-6 would have been missed if the testing had been performed only on the peripheral blood. The median viral load was 3.84 log 10 copies/10^6 cells.

In a retrospective study of 121 liver transplant patients, HHV-6 infection was considered the cause of hepatitis after liver transplantation in 8 (6.7%) patients, demonstrated by serology and immunostaining of HHV-6 antigens in liver biopsy specimens.[32] Two patients presented with a pure HHV-6 infection (without concomitant CMV infection or rejection), both of whom had significant graft dysfunction. Of the eight patients, five demonstrated acute rejection and lymphocytic infiltration was observed in three patients.

3.4 | Encephalitis

HHV-6 encephalitis is most often seen in cord blood (8%-10%) and stem cell transplant patients (1%-3%),[33–35] but it has also been reported in several liver transplant recipients. A retrospective review of medical and laboratory records reported a correlation between HHV-6 infection and symptoms of encephalitis in seven (35%) of 20 liver transplant patients.[36] A case was reported in which a patient, transplanted for liver failure because of HCV, presented with fever, an erythematous macular rash on his trunk and back, mental confusion, agitation and visual hallucinations.[37] Using nucleic acid testing, HHV-6 was detected in his plasma and cerebrospinal fluid (CSF). Testing was negative for CMV and EBV. Brain MRI demonstrated symmetric high signal intensity in the medial temporal lobes involving the bilateral amygdala and hippocampi, indicative of HHV-6 encephalitis. The patient was successfully treated with foscarnet and a reduction in immunosuppression. He had no significant neurological sequelae at 1-year follow-up. Two other case reports documented encephalitis after liver transplantation.[38,39] Both patients were diagnosed with encephalitis after their CSF tested positive for HHV-6 by PCR and other pathogens were ruled out and both were successfully treated with intravenous ganciclovir.

In 2011, a case of ganciclovir-resistant HHV-6 encephalitis in a liver transplant patient was reported.[40] This patient was on IV ganciclovir because of primary CMV disease until re-admission 2 months post-transplant when he presented with tonic-clonic seizures, altered mental status, agitation and neutropenia. CSF and plasma were positive for HHV-6 by PCR and brain MRI revealed prominent multifocal T2 hyperintensities in the left mesial temporal lobe, pons and cerebellum, as well as bilateral parietal occipital hyperintensities. Since he acquired the infection while on IV ganciclovir, the patient was treated with foscarnet, with clinical improvement.

3.5 | Gastrointestinal Disease

HHV-6 infection in liver transplant patients can present as colitis.[41] In a retrospective study of 1345 patients who underwent HHV-6 PCR testing at a French hospital between May 2003 and December 2004, 43 samples from 25 patients (3%) were positive for HHV-6.[41] Nine of the 25 (36%) patients experienced gastrointestinal symptoms, including 6 (67%) who presented with colitis, three of whom underwent liver transplantation. Another study analysed the gastroduodenal mucosa of biopsy samples obtained from 90 liver transplant recipients for HHV-6 antigens.[42] The researchers detected HHV-6 antigens in 21 patients, of whom 15 displayed simultaneous HHV-6 antigenaemia. Histopathological findings in the HHV-6-positive mucosa were nonspecific and included very mild inflammation.

3.6 | Myelosuppression and Pneumonia

Myelosuppression has been attributed to HHV-6 reactivation.[43–45] In a report of four liver transplant recipients, HHV-6 reactivation occurred a median of 50 days post-transplant. Severe cytopenia was observed in all patients and leucopenia was the most commonly effected bone marrow lineage.[27] HHV-6-associated interstitial pneumonitis occurred in one of the four patients.[27] HHV-6 was documented by immunohistochemical staining of lung tissue. No other pathogens were detected in the lungs, blood or bone marrow of these four patients.

3.7 | CMV co-infection and disease

Several studies have observed an association between HHV-6 infection and CMV disease (Table 1). HHV-6 antigenaemia regularly precedes CMV antigenaemia and has been implicated as the probable cause of graft dysfunction.[46] A 2012 study of 45 liver transplant recipients reported CMV infection in 23 (51.1%) and HHV-6 infection in 12 (26.7%) patients.[47] Of the six patients who displayed an acute cellular rejection episode, four had concomitant bacterial infections and three experienced graft rejection episodes.[47] Those who reactivated HHV-6 were 3.5 times (P=.02) more likely to suffer from severe CMV-associated disease.[48] In a prospective study of 33 consecutive liver transplants, HHV-6 was detected in PBMCs by qualitative PCR in 11 (33%) patients.[49] As is common with ubiquitous viruses, the association between CMV and HHV-6 was stronger when quantitative viral load, rather than qualitative DNA detection, was utilized. While high HHV-6 viral loads were detected in 3 (27%) of 11 CMV donor+/recipient- patients, high HHV-6 levels were not detected in either 15 CMV donor+/recipient+ or 7 CMV donor-/recipient- patients (P=.037).[49] Of the 10 patients who had symptomatic CMV disease, four had high HHV-6 levels (P=.02), and eight had either high HHV-6 or HHV-7 levels (P<.0001).[49] The results from these studies strongly suggest an interaction between β-herpesviruses, particularly HHV-6 and CMV. Symptoms primarily attributed to CMV may be the result of a co-infection and not just the effects of a CMV infection per se.

3.8 | Hepatitis C disease progression

One study observed that patients who underwent liver transplantation for cirrhosis caused by HBV or HCV were more likely to have an HHV-6 infection (P=.025).[8] However, the relationship between HHV-6 and HCV is still not clearly defined and some studies[50,51] have observed no association between HCV recurrence and HHV-6 viral load. A study detected HHV-6 DNA in 9/12 (75%) patients who suffered HCV recurrence (P=.049).[52] HHV-6 is also associated with higher fibrosis scores (Table 1). Patients undergoing liver transplantation for cirrhosis caused by HBV or HCV are more likely to have post-transplant HHV-6 reactivation detected in the blood.[8]

TABLE 1 Indirect Effects of HHV-6 Infection

Condition	Pts	*P*-Value (<.05)	Univariate or multivariate	Notes	Refs.
Graft dysfunction & graft survival	170	.014 .003	Univariate	High liver biopsy HHV-6 DNA levels (>75th percentile, 11.27 copies/1000 cells) and detection of HHV-6 in the peripheral blood were significantly associated with decreased graft survival after diagnosis of graft hepatitis (*P*=.014 and *P*=.003, respectively, median follow-up was 23.8 months).	[59]
	41	.004	Univariate	HHV-6 was associated with rejection in 41 patients with rejection after 30 days. (*P*=.004). HHV-6 was not associated with overall rejection (mean 13.5 days) since HHV-6 mean reactivation occurred later (27 days).	[26]
CMV disease	200	.003	Univariate	CMV viral load was significantly higher in patients with HHV-6 infection versus those without (*P*=.003).	[26]
	88	.013 .001	Univariate Univariate	Symptomatic CMV disease was more common in patients with HHV-6 infection than it was in those without infection (*P*=.013). CMV viral load was higher in those with HHV-6 infection (*P*=.001)	[96]
	88	.013	Multivariate	HHV-6 infection remained an independent risk factor for CMV disease.	
	33	.022	Univariate	This association with high levels (>5000 copies/PCR input) of HHV-6 and HHV-7 but not with qualitative detection.	[49]
	41	.0128	Univariate	There was a statistically significant difference in the presence of HHV-6 DNA in pre-transplant graft biopsies between recipients who showed and did not show CMV disease after liver transplant (*P*<.0128).	[52]
	139	.01	Univariate	HHV-6 reactivation was associated with CMV disease (*P*=.01) and severe CMV-associated disease (*P*=.01).	[48]
	139	.02	Multivariate	HHV- 6 reactivation remained significant in multivariate analysis (RR, 3.5; 95% CI, 1.2–10.2; *P*=.02)	
HCV higher fibrosis score, recurrence	51	.01	Univariate	Patients with HHV-6 viraemia had a significantly higher fibrosis score upon HCV recurrence (mean 1.5 vs 0.3, *P*=.01).	[97]
	66	.01	Univariate	HHV-6 infection was associated with the development of more severe recurrence (hepatitis and/or fibrosis score>2) (*P*=.01).	[98]
	66	.031	Univariate	Fibrosis scores at last follow-up were higher in patients with CMV disease and in patients with HHV-6 infection (*P*=.031).	
	170	.031	Univariate	Fibrosis scores at follow-up were higher in patients with HHV-6 infection (1.18 vs 0.55; *P*=.031).	[59]
Opportunistic infection	200	.001 .001	Univariate Multivariate	Risk of opportunistic infection increased by 1.47 per log10 increase in HHV-6 viral load (*P*=.001). In a multivariate analysis designed to control for the level of immunosuppression, the risk of opportunistic infection increased by 3.68-fold in patients with HHV-6 infection (*P*=.001)	[28]
	80	.03	Univariate	HHV-6 infection was an independent predictor of invasive fungal infections (odds ratio 8.3, *P*=.03)	[55]
Mortality	170	.003	Univariate	Detection of HHV-6 DNA in blood samples was associated with a shorter survival in Kaplan Meier analysis (*P*=.003 log rank).	[59]
	67	.0118	Univariate	11/26 (42.3%) of HHV-6 reactivated recipients died compared to only 6/41 (14.6%) without reactivation	[8]
	67	.0114	Multivariate	HHV-6 reactivation was an independent risk factor for increasing the mortality (*P*=.014)	
	80	.04 .008	Univariate Univariate	Mortality rate at 3 months in patients with HHV-6 infection was significantly higher than those without HHV-6 infection (*P*=.04). This association was even more significant at last follow-up (29% mortality in HHV-6+ patients vs 6% mortality in HHV-6- patients) (*P*=.008)	[55]

3.9 | Immunosuppression resulting in fungal and opportunistic infections

HHV-6 can counter the human immune system's ability to eradicate the virus in many ways[45,53] and is thought to impact the occurrence of opportunistic infections in patients after liver transplantation.[44] Liver transplantation has been shown to suppress HHV-6-specific memory response and in one study, only one (7%) of 15 liver transplant patients exhibited an effective proliferative response at 2 weeks compared to 64% matched healthy subjects. This deficit persisted at 2-3 months and at 1-year post-transplant, with only 25% of patients exhibiting an HHV-6-specific memory response, whereas the recovery of the memory response to CMV was much more robust. The lack of T-helper cell response to HHV-6 was not because of overall reduced responsiveness where the patients lacked the ability to respond to any or all stimuli.[54] HHV-6s immunosuppressive effect has been confirmed in recent studies.[45]

A study of 200 liver transplant recipients demonstrated HHV-6 infection was associated with opportunistic infections, including CMV, EBV-related post-transplant lymphoproliferative disease, VZV, invasive fungal infections and mycobacterial disease.[28] Multivariate analysis showed that the risk of opportunistic infection increased by 1.47 per $\log_{10}$ increase in HHV-6 viral load (P=.001). HHV-6 was the only predictive factor of opportunistic infections excluding CMV (odds ratio 3.33; 95% CI 1.55-7.14; P=.002).[28] Another prospective study found that HHV-6 infection was an independent predictor of invasive fungal infection in a cohort of 80 consecutive liver transplants (odds ratio 8.3, 95% CI 1.2-58.0, P=.03).[55] Furthermore, a prospective study of 548 liver transplant recipients detected ciHHV-6 in seven patients, low-level DNAemia in 35 patients and no HHV-6 DNAemia in 506 patients prior to transplant.[21] Bacterial infection was significantly more common in the ciHHV-6 group compared to the group without HHV-6 (71.4% vs 31.4%, P=.04).

3.10 | Allograft rejection and survival

HHV-6 infection in the liver allograft increases expression of adhesion molecules[56,57] on vascular endothelial cells and infiltrating leucocytes, which could lead to local inflammation and graft damage and result in graft dysfunction or rejection.[58] A study of 170 adult liver transplant recipients with graft hepatitis demonstrated that high intrahepatic HHV-6 DNA levels (P=.014) and HHV-6 DNAemia (P=.003) were significantly associated with decreased graft survival.[59] The probability of graft survival was less than 60% at 500 days in those with high HHV-6 levels in the liver graft (>75th percentile: 11.27 copies/10^3 cells) and was only 40% at 500 days in those with HHV-6 found in the peripheral blood (compared to over 80% in controls). A study of 200 patients using qualitative PCR found that HHV-6 in the plasma was not associated with graft rejection when early rejections (mean 13.5 days) before HHV-6 reactivation (mean 27 days) were included. However, when 41 cases of rejection post day 30 were analysed, HHV-6 viral load was an independent predictor of rejection (odds ratio 2.27, 95% CI 1.09-4.77; P=.029).[28] A study of 59 liver transplant patients found that HLA-DR15 was associated with HHV-6 positivity in donor biopsies and that patients with HLA-DR15 in liver donor biopsies developed more rejection after liver transplantation.[60] In a study of 33 paediatric liver transplant recipients, HHV-6 was detected in 3 (9.1%) patients and HHV-6 infection was associated with concurrent episodes of moderate to severe acute graft rejection in two of the three children.[15] Finally, a prospective study of 548 liver transplant recipients reported a higher rate of allograft rejection in patients with ciHHV-6 (71.4%) compared to patients with low level HHV-6 DNAemia (37.1%) and patients with no HHV-6 DNAemia (42.9%).[21]

3.11 | Mortality

All-cause mortality is higher in patients after liver transplantation with HHV-6 reactivation or infection (Table 1).[8,55,59] A Japanese study[8] of 67 liver transplant recipients found that mortality was significantly higher at the last follow-up among patients with HHV-6 reactivation (P=.0118) and that HHV-6 reactivation was an independent risk factor for increasing mortality (P=.014). Another study reported that mortality rate at 3 months in patients with HHV-6 infection was significantly higher than that of patients without HHV-6 infection (P=.04). This association was even more significant at last follow-up (29% mortality in HHV-6+ patients vs 6% mortality in HHV-6- patients; P=.008).[55]

4 | RISK FACTORS ASSOCIATED WITH ACTIVE HHV-6 INFECTION IN LIVER TRANSPLANTATION

4.1 | HHV-6 seronegativity

The frequency of HHV-6 seronegativity in adult solid organ transplants is very low (3.6%) and the risk of HHV6 disease is low.[61] In contrast, HHV-6 seronegativity is higher in paediatric liver transplant patients and an important factor for primary HHV-6 infection. One study found that five out of six (83%) seronegative paediatric living-related liver transplant recipients developed primary HHV-6 infection after transplantation.[24] A study conducted in a large paediatric transplant centre found that 27 of 66 (40.9%) paediatric liver transplant recipients were seronegative for HHV-6 pretransplant.[62] Of 18 seronegative patients tested after transplant, nine (50%) developed HHV-6 primary infection, whereas of 24 seropositive patients tested, only five (17.2%) developed HHV-6 reactivation.[62] This study determined that HHV-6 seronegative liver transplant patients presented HHV-6 infection earlier (median: 2 weeks, range: 2 weeks-2 months) than HHV-6 seropositive patients (median: 2.5 months, range: 3 weeks-9 months) and that HHV-6 seronegative patients had more severe symptoms.

In general, the frequency of HHV-6 plasma viraemia is lower in adult liver transplant recipients than in paediatric liver transplant recipients.[8] One key study directly compared a group of 17 paediatric liver transplant recipients to 17 adult liver transplant recipients and found that only 11.8% of adults presented with HHV-6 viraemia compared to 29.4% of children.[63] One study reported that 49% of paediatric liver transplant recipients experienced HHV-6 plasma viraemia (reactivation) even though 85% of them were seropositive for HHV-6 at the time of transplantation (Tables 2 and 3).[24]

TABLE 2 Frequency of HHV-6 viraemia in liver transplant patients[l]

References	Year	Paediatric or adult	Plasma/whole blood/PBMCs	Prophylaxis	Total liver transplant patients	HHV-6 reactivated	% Reactivated	Median HHV-6 viral load (range)
[96]	2014	Paediatric	Plasma	GCV/VGV	23	1	4.3%	n/a
[15]	2003	Paediatric	Plasma	GCV	33	3	9.1%	25 copies/mL (22-77 copies/mL)
[24]	2000	Paediatric	Plasma	ACV	47	23	48.9%	n/a
[63]	2008	Paediatric	Plasma	None	17	5	29.4%	Range: 1.4-2.8 × 104 copies/mL
		Adult			17	2	11.8%	
[8]	2008	Adult	Plasma	ACV	67	26	38.8%	n/a
[50][c,g]	2002	Adult	Plasma	ACV/GCV[k]	90[k]	36[k]	40.0%	n/a
Totals for plasma					294	96	33%	
[26][a]	2008	Paediatric	PBMCs	n/a	23	7[b]	30.4%	571 copies/10^6 cells (58-10, 526 copies/10^6 cells)
[31][e]	2013	Adult	PBMCs	ACV/GCV/VGV[e]	15	2	13.3%	2.97-3.20 $\log_{10}$ copies/10^6 PBMCs
[28][h]	2002	Adult	PBMCs	GCV[h]	200	56	28.0%	2.3 $\log_{10}$ copies/μg input DNA (0.48 to >$\log_{10}$ copies//μg input DNA)
[23][c]	2011	Adult	PBMCs	ACV/GCV	30	12	40.0%	n/a
[97][d,g]	2002	Adult	PBMCs	n/a	51	21	41.2%	n/a
[99][c,j]	2000	Adult	PBMCs	GCV[j]	88	48	54.5%	n/a
Totals for PBMCs					407	139	34%	
[29]	2014	Paediatric	Whole blood	GCV	154	25	16.2%	n/a
[51][f]	2007	Adult	Whole blood	GCV/VGV	42[f]	2	4.8%	Range for all HCV+ patients: 0-450 copies/mL
					77[f]	11	14.3%	Range for all HCV- patients: 0-31,020 copies/mL
[49][c]	2001	Adult	Whole blood	ACV	33	11	33.3%	Range: 50-5 × 10^4 copies/DNA input
[14]	2015	Adult	Whole blood	GCV/VGV	64	23	35.9%	2.61 $\log_{10}$ copies/mL (IQR 2.18-3.69)
Totals for whole blood					370	72	19%	

[a]Contains four groups of children: Fulminant hepatic failure of unknown cause (n = 6), fulminant hepatic failure of known cause (n = 4), acute decompensation of chronic liver disease (n = 3), chronic liver disease (n = 10); the rate of detection was 10/13 (77%) in the first three groups vs 2/10 (20%) in the last group.

[b]Of the 12 patients who were HHV-6 positive in liver biopsy, only seven had HHV-6 detected in PBMCs.

[c]Detected using qualitative PCR.

[d]Used a shell vial culture assay to detect immediate early antigen of HHV-6.

[e]HHV-6 graft hepatitis was diagnosed via liver biopsy and PBMCs were available for 15 patients (out of 26 possible patients): HHV-6 was detectable in 2/7 patients with HHV-6-positive graft hepatitis and in 0/8 with HHV-6-negative graft hepatitis.

[f]Study population included 177 CMV D+/R- liver transplant patients who were part of a larger study that evaluated CMV prophylaxis. The 177 patients were stratified into two groups: 42 HCV-positive patients and 77 HCV-negative patients.

[g]Study group included only HCV-positive patients.

[h]Patients on GCV prophylaxis had a lower incidence of HHV-6 infection (4/31 [12.9%]) compared with those patients who did not receive ganciclovir prophylaxis (52/169 [30.8%]) (*P*=.042).

[j]CMV donor-negative/recipient-negative patients were excluded from this study. Only CMV D+/R-subgroup received GCV (n = 7).

[k]Only the 14 CMV D+/R- (15.21%) patients received CMV prophylaxis; of the 36 patients who reactivated HHV-6, four received CMV prophylaxis (see Table 3).

[l]Several of the values in the table below are not indicative of typical frequencies of HHV-6 viraemia in liver transplant patients. Some studies include only patients at higher risk for HHV-6 reactivation, whereas other studies include patients who received antiviral prophylaxis (GCV, ganciclovir; VGV, valganciclovir; ACV, acyclovir) thus lowering the frequency of viraemia.

TABLE 3 Frequency of HHV-6 Viraemia in liver transplant patients (separated by CMV Prophylaxis [GCV/VGV])

References	Prophylaxis	Total liver transplant patients	HHV-6 Reactivated	% Reactivated
[96]	GCV/VGV	23	1	4.3%
[15]	GCV	33	3	9.1%
[50][c,g]	GCV	14	3	21.4%
[28][h]	GCV	31	4	12.9%
[29]	GCV	154	25	16.2%
[51][f]	GCV/VGV	177	13	7.3%
[14]	GCV/VGV	23	1	4.3%
Totals for CMV prophylaxis		455	50	11%
[28][h]	None	169	52	30.8%
[50][c,g]	ACV	76	33	43.4%
[24]	ACV	47	23	48.9%
[8]	ACV	67	26	38.8%
[49][c]	ACV	33	11	33.3%
[14]	None	41	22	53.7%
Totals for no CMV prophylaxis		433	167	39%

Reference [31] was omitted from this table due to insufficient data regarding prophylaxis administered to the two patients who had HHV-6 detected in PBMCs. Reference [22] was omitted from this table due to insufficient data regarding which patients received ACV/GCV vs ACV only. Reference [93] was omitted from this table because it is a study of a subset of the population in reference 27, which has been included in this table.

4.2 | Immunosuppressive Agents

A study of 92 HCV-infected liver transplant recipients reported that patients with HHV-6 reactivation received higher doses of steroids (P=.032).[50] Hydrocortisone activates HHV-6 in vitro[64] and studies of cases of severe drug hypersensitivity have shown that patients receiving systemic corticosteroids disproportionately reactivate HHV-6 compared to EBV and CMV.[65]

T-cell defects are associated with HHV-6 reactivation. For example Muromonab-CD3 (OKT3) is an immunosuppressant drug previously used to reduce acute rejection in liver transplant patients. A retrospective analysis of serial serum samples drawn from 139 liver transplant recipients involved in a prospective trial on CMV reported that the use of OKT3 for rejection treatment was significantly associated with HHV-6 reactivation, defined as a four-fold increase in HHV-6 IgG and/or the presence of HHV-6 IgM.[48] Thirty-six (41.4%) of 87 patients with HHV-6 reactivation received OKT3 versus 11 (21.2%) of 52 without HHV-6 reactivation (P=.02).

4.3 | Pre-transplant HHV-6 reactivation

Pretransplant hepatic HHV-6 infection in patients with acute liver failure (ALF) may be a risk factor for HHV-6 infection of the liver graft post-transplant. Several studies have identified HHV-6 reactivation in patients with ALF of unknown cause, but not in patients with liver failure with known aetiology. In a study of 32 liver explants for ALF patients, HHV-6 antigens were detected, using immunoperoxidase staining, in both hepatocytes and infiltrating lymphocytes in the portal area of 12 (80%) of 15 patients who underwent liver transplantation owing to ALF of unknown cause. HHV-6 antigens were observed in only four (23.5%) of 17 control patients with a known cause of ALF.[66] The predominant histological finding of HHV-6 infection was moderate to severe portal lymphocytic infiltration although some hepatocytes were also antigen-positive. Notably, 80% of patients with HHV-6 positive explants also showed evidence of HHV-6 reactivation in testing prior to the transplant.[66] In a follow-up study,[67] researchers found HHV-6 in nine (50%) of the 18 post-transplant biopsies. No post-transplant HHV-6 infections were observed in patients without evidence of HHV-6 in their pretransplant biopsies.

4.4 | Inherited chromosomally integrated HHV-6 (ciHHV-6)-positive donor organs & recipients

Although further study is required, it is possible that active HHV-6 infection could be transmitted horizontally by donated ciHHV-6-positive organs. Two such cases were reported at the 9th International HHV-6 Conference in 2015.[68] Sequencing of the DNA confirmed that in both cases, the virus of the donor liver could be found in several compartments of the recipient. In the first patient, a 5-year-old receiving a ciHHV-6B+ liver, the persistent HHV-6B plasma viraemia (1.8×10^3 – 3.6×10^3 copies/mL) that developed 18 months post-transplant was suspected to correspond to incidental ciHHV-6B hepatocyte lysis rather than production of infectious particles by infected cells. The second patient, a 53-year-old with cirrhosis who acquired HHV-6A from the transplant, had very high viral loads of HHV-6A in CSF and gastrointestinal tract, suggesting a massive reactivation associated with delirium and profuse diarrhoea.

TABLE 4 HHV-6 Detection in biopsy vs blood

References	Method	Biopsy details	Total patients tested (Biopsy)	Positive biopsy results	% Biopsy	Total patients tested (Blood)	Positive blood results	% Blood	Notes
[26]	Real-time PCR (quantitative)	Snap-frozen biopsy specimen from time of transplant.	6	5	83.3%	6	3	50.0%	Group 1[a]
			4	2	50.0%	4	2	50.0%	Group 2[a]
			3	3	100.0%	3	1	33.3%	Group 3[a]
			10	2	20.0%	10	1	10.0%	Group 4[a]
[59]	Real-time PCR (quantitative)	Percutaneous liver biopsy in patients with graft hepatitis	170	99	58.2%	126	12	9.5%	126/170 patients had PBMCs tested
[31]	Real-time PCR (quantitative)	Frozen sample from native liver or from explanted liver	26	10	38.5%	15	2	13.3%	15/26 patients had PMBCs tested.
[66]	Antigen test	Explanted liver biopsy from failed liver transplant	15	12	80.0%	12	10	83.3%	Positivity determined via antigen test
Totals			234	133	56.8%	176	31	17.6%	

[a]Group 1: Children with fulminant hepatic failure (FHF) of undetermined cause. Group 2: Children with a recognized cause of FHF. Group 3: Children with acute decompensation of chronic liver disease. Group 4: Children with chronic liver disease.

5 | DIAGNOSIS

5.1 | Polymerase chain reaction (PCR)

Laboratories in North America and Japan typically use real-time quantitative PCR on plasma whereas in Europe whole blood testing is more common. PCR can be performed on whole blood, plasma, PBMCs and biopsy tissue samples. Most centres view any HHV-6-positive result in plasma or CSF as a sign of clinically significant active infection, whereas whole blood assays require a threshold to determine a meaningful clinical reactivation.[69] Using PCR, the frequency of HHV-6 detection in plasma (33%) vs PBMCs (34%) from liver transplant patients is essentially the same (Table 2), whereas the rate for whole blood (19%) is lower. HHV-6 viral loads in liver transplant patients vary (Table 2) and CMV prophylaxis greatly affects the frequency of HHV-6 reactivation (Table 3). HHV-6 is highly cell-associated and HHV-6 DNA may not be detectable or elevated in plasma or PBMC testing, in spite of a persistent infection.[31] In persistent HHV-6 infections, only biopsy analysis can rule out an HHV-6 infection. Buyse et al. found two distinct patterns in liver biopsies of patients positive for HHV-6: (i) those with a high viral load (4 $\log_{10}$ copies/10^6 cells) had severe periportal activity; (ii) those with a lower viral load had lobular activity with mild to moderate portal inflammatory infiltrates.[31]

Patients with persistently high levels of plasma DNA should be tested for ciHHV-6 using whole blood or PBMCs. Whole blood HHV-6 DNA levels above log 5.5 copies/ml should be assumed to be ciHHV6. Any level of HHV-6 DNA in CSF could be assumed to be from an active infection and treatment should be considered if symptoms are suggestive of HHV-6 encephalitis. Patients positive for ciHHV-6 may have a low level of HHV-6 DNA in CSF owing to normal cell lysis. If there are a large number of cells as a result of blood in the CSF sample, the viral load can be significant.

Although PCR assays are commercially available, they are still outnumbered by in-house developed assays,[70] resulting in inconsistent diagnostic testing. An international study comparing HHV-6 PCR assays from 51 different laboratories revealed extensive interlaboratory variation in quantitative PCR results, with the standard deviation ranging from 0.5 $\log_{10}$ copies/mL to 0.7 $\log_{10}$ copies/mL. All the commercial assays reported correct results, compared to 96.1% of the in-house real-time assays and conventional in-house assays, suggesting that commercial assays may have a higher sensitivity.[71] In addition, HHV-6 PCR results are variably reported as copies/mL plasma or per one million peripheral blood lymphocytes.[72] Clinically significant HHV-6 DNA levels remain to be determined in liver transplant recipients.[26,59,63] Pischke et al. suggested that high intrahepatic viral loads (>11.27 copies/1000 cells was an independent factor associated with decreased graft survival.[59] International laboratory standards do not exist but are currently in development.[70]

5.2 | Liver biopsy tissue testing

Detection of HHV-6 DNA in the patient's plasma or CSF indicates an active infection. However, HHV-6-associated liver disease

TABLE 5 Antiviral therapy in liver transplant recipients

Antiviral treatment	Age/sex	Indication for treatment/key findings	Imp.[d]?	Refs.
Valganciclovir	16 years/M	14 611 copies HHV-6 DNA/10^6 cells in liver biopsy. Fever, abnormal liver tests, hepatitis/severe portal inflammation, severe periportal necrosis, moderate lobular necrosis, <5% confluent necrosis.	Yes	[31]
	60 years/M	Positive HHV-6 viraemia. Elevated liver enzymes, fatigue, malaise, dizziness, abdominal bloating.	Yes	[100]
Intravenous ganciclovir	10 months/M	HHV-6 load in liver biopsy: 8125 copies/10^6 cells, HHV-6 Load in PBMCs: negative. Fever + macular rash (15 days), elevated liver enzymes, abnormal bilirubin.	Yes	[26]
	8 months/M	HHV-6 load in liver biopsy: 1371 copies/10^6 cells, HHV-6 Load in PBMCs: 6643 copies/10^6 cells. Fever (4 days), elevated liver enzymes, abnormal bilirubin.	No	
	7 months/M	HHV-6 load in Liver biopsy: 13 768 copies/10^6 cells, HHV-6 Load in PBMCs: 10 000 copies/10^6 cells. Fever (3 days), elevated liver enzymes, abnormal bilirubin.	No	
	43 years/M	44 000 gEq HHV-6A/μg of DNA in paraffin embedded liver biopsy sample. Fever, mild neutrophil leucocytosis, elevated liver enzymes, syncytial giant-cell hepatitis.	Yes	[30]
	44 years/F	12 434 copies HHV-6 DNA/10^6 cells. Hepatitis, fever, elevated liver enzymes/moderate portal inflammation, severe periportal necrosis, 10% confluent necrosis, moderate lobular necrosis.	Yes	[31]
	61 years/M	CSF was positive for HHV-6. Confusion, diffuse erythematous cutaneous rash/MRI brain showed bilateral and symmetrical increased T2 signal, with non-enhancing lesions in the temporal lobe and hippocampal gyrus of both hemispheres. Skin biopsy was compatible with GVHD.	Yes	[38]
	49 years/M	CSF was positive for HHV-6. Fever, confusion, occipital headaches, involuntary movements of the arms and legs.	Yes	[39]
	7 months/F	HHV-6 Antibody Titres (peak levels): IgG 32, IgM 8. HHV-6 PCR was positive on day 14 via nested-PCR, fever (day 5-12)	Yes	[79]
	8 months/F	Peak HHV-6 DNA in liver biopsy was >1000 copies/10^5 PBMCs; peak HHV-6 DNA in plasma was 10-100 copies/10^5 PBMCs. Fever, petechiae, leucopenia, thrombocytopenia, elevated liver enzymes.	Yes	[90]
Intravenous ganciclovir/valganciclovir	58 years/F	15 096 copies HHV-6 DNA/10^6 cells in liver biopsy. Elevated liver enzymes/moderate portal inflammation, moderate periportal necrosis, mild lobular necrosis.	Yes	[31]
	38 years/F	7036 copies HHV-6 DNA/10^6 cells in liver biopsy. Abnormal AST/severe portal inflammation, severe, periportal necrosis, moderate lobular necrosis.	Yes	
Cidofovir/valganciclovir	45 years/M	198 000 copies HHV-6 DNA/10^6 cells in liver biopsy. Leucopenia, abnormal liver enzymes/Mild portal inflammation, moderate lobular necrosis.	Yes	[31]
Cidofovir	2.3 years/F[a]	HHV-6 DNA was detected in leucocytes, pleural effusions, BAL and liver biopsy. High fever, necrotic hepatitis, graft dysfunction, respiratory failure, pneumonitis, pleural effusion, highly inflammatory skin rash.	Yes	[25]
Ganciclovir/foscarnet	55 years/M	183 000 HHV-6 DNA copies/mL in plasma, 7300 HHV-6 DNA copies/mL in CSF. Fever, erythematous macular rash on trunk and back, confusion, agitation, visual hallucinations, leucopenia, mild thrombocytopenia/MRI brain showed symmetric high signal intensity in the medial temporal lobes involving the bilateral amygdala and hippocampi consistent with HHV-6 encephalitis.	Yes	[37]
	71 years/M[b]	1162 HHV-6 DNA copies/mL CSF; 252 240 HHV-6 DNA copies/mL plasma. Tonic-clonic seizures, altered mental status, agitation and inability to protect his airway, cough/abnormal EEG. MRI brain revealed multifocal T2 hyperintensities most prominent in the left mesial temporal lobe, pons and cerebellum, as well as bilateral parietal occipital hyperintensities.	Yes	[40]
	43 years/M	Lumbar puncture in December 2000 revealed positivity for HHV-6 at 7992 gc/mL. Plasma HHV-6 levels in July 2007 was 7364 gc/mL. Fever, diarrhoea, worsening HHV-6 viraemia despite antiviral therapy. Quantification of HHV-6 on hair resulted 11 159 420 gc/10^6 cells, consistent with ciHHV-6.	No	[82]

(Continues)

TABLE 5 (Continued)

Antiviral treatment	Age/sex	Indication for treatment/key findings	Imp.[d]?	Refs.
Acyclovir[c]/ intravenous ganciclovir	32 years/F	171 959 HHV-6 DNA copies/10^5 cells in liver biopsy, consistent negative HHV-6 tests in PBLs. Influenza-like syndrome with fever, associated with a non-specific skin rash, jaundice, abnormal liver enzymes and bilirubin levels, hepatic encephalopathy.	Yes	[11]
Totals	19 patients		16/19 (84%)	

[a]Patient showed enhanced body weight normalized clearance of cidofovir and required a dosage increase from 5 mg/kg/week to 12 mg/kg/week.
[b]Patient acquired HHV-6 infection while on ganciclovir for CMV infection and was subsequently treated with foscarnet.
[c]Acyclovir is not active against HHV-6.
[d]Improvement is defined as the resolution of symptoms after antiviral therapy and no HHV-6 disease-associated mortality.

cannot be ruled out in the absence of a biopsy even when there is no detectable viraemia.[11,26,31] Within the same patient groups, the rates of detection have been approximately 56.8% in tissue biopsies (range 20% to 100%) vs only 17.6% in blood samples (range 10% to 83.3%) (Table 4). If HHV-6-induced liver dysfunction is suspected, liver tissue will be more revealing than plasma or serum, although both should still be tested for HHV-6. Taking up to three biopsy specimens can improve diagnostic yield.[73] This is true with other organs as well, especially during persistent infections: HHV-6 DNA can be found in lung biopsies but not the plasma of patients with "idiopathic" pneumonia syndrome after lung transplantation[74] and high levels of DNA can be found in biopsy tissues of patients with persistent HHV-6 myocarditis, in spite of little or no DNA in the plasma.[9]

Immunohistochemical (IHC) staining of biopsy specimens can determine if the virus was active by staining for viral proteins.[66] It is also possible to use virus-specific monoclonal antibodies to distinguish between HHV-6A and HHV-6B variants. Fluorescent in situ hybridization (FISH) can be used to isolate HHV-6 positive cells.[75] In FISH, fluorescent probes are hybridized to specific sequences of the HHV-6 genome in the tissue sample and fluorescence microscopy is then used to locate the where the probe is bound to the genome. Both IHC and FISH are useful for localizing the virus to specific cells and FISH can identify the cellular distribution of HHV-6 DNA.

HHV-6B has been detected in hepatocytes by in situ hybridization (ISH)[13,76,77] and was found to be more prominent in hepatocytes than in intrahepatic mononuclear cells in two studies.[13,76] In one patient, ISH localized DNA and RNA in the hepatocyte nuclei and envelope antigen was detected in the hepatocyte cytoplasm.

HHV-6B has been found in sinusoidal mononuclear cells[13,46] and in the nuclei of epithelial cells in the intrahepatic bile ducts.[76,77] One study detected viral RNA in the nuclei of hepatocytes, but did not observe positive signals for DNA or RNA in infiltrating lymphocytes or other cell types in either biopsy specimens or in control patients.[76]

5.3 | Antigenaemia test

HHV-6 antigens can be detected in both whole blood and tissue biopsy specimens.[16,66] The antigenaemia test is based on demonstration of HHV-6 antigens in PBMCs using specific monoclonal antibodies and immunoperoxidase staining. The same method can be used for histochemical staining to detect HHV-6 antigens in liver biopsies. Antigen testing can indicate active infection and distinguish HHV-6A and HHV-6B, although it is labour intensive, semi-quantitative and not commercially available.[58,78]

5.4 | Serology

Although serological assays for HHV-6 are available for clinical use, they are not widely used in the liver transplant setting. Assays include immunofluorescence assays (IFA) and enzyme-linked immunosorbent assay (ELISA). Positive HHV-6 IgM antibodies indicate active infection[48]; they appear transiently 2-4 weeks after primary infection or acute reactivations,[79] but do not persist in chronic infections. Thus, anti-HHV-6 IgM is of limited value for diagnosing HHV-6 reactivation in adult patients. In primary infection and acute reactivation IgG antibody titres typically increase four-fold within 4-6 weeks.[24,80] IgG serology cannot distinguish between HHV-6A and B.

5.5 | Identifying inherited chromosomally integrated HHV-6 (ciHHV-6)

It is important to consider the possibility of inherited chromosomally integrated HHV-6 in any patient with a persistently high HHV-6 viral load. Determining ciHHV-6 status will help the physician make a more informed decision on antiviral treatment, which is sometimes unnecessary or prolonged. Determining ciHHV-6 status can alert the physician to cease further qPCR DNA testing as ciHHV-6+ patients will consistently have high background levels of HHV-6 DNA. Screening can be done with a quantitative whole blood PCR DNA test. HHV-6 levels in whole blood that exceed 5.5 $\log_{10}$ copies/mL can be assumed to be ciHHV-6[20] and organs will have ≥1 HHV-6 genome/cell. Droplet digital PCR testing[81] or a positive qualitative test of HHV-6 in hair follicles or fingernails can confirm the diagnosis.[20] Failure to recognize ciHHV-6 can result in patients being treated unnecessarily with toxic antivirals.[82] HHV-6 mRNA testing, can determine if HHV-6 is actively replicating. Some experts have called for screening of all patients and donor organs or cells for ciHHV6.[83,84] Although antiviral therapy has been associated with clinical improvement of ciHHV-6+ patients,[19,85–87] a report of 21 transplant recipients, including five liver and two combined liver-kidney, highlights the common misdiagnosis of ciHHV-6 as active HHV-6 infection.[88]

6 | TREATMENT AND PREVENTION

Clinically significant HHV-6 infections in liver transplant patients can be treated with antiviral drugs and a reduction in immunosuppressive therapy. However, there are currently no FDA-approved antiviral drugs for the treatment of HHV-6 infection. Ganciclovir, cidofovir and foscarnet have shown efficacy against HHV-6 in vitro[89] and are used to treat HHV-6 in the clinical setting (Table 5). Of the 19 case reports included in Table 5, 16 (84%) improved after antiviral therapy.

6.1 | Ganciclovir (GCV) and valganciclovir (VCV)

Ganciclovir and valganciclovir are the most treatments for HHV-6 infection in liver transplant patients.[30,38,90] HHV-6 strains with mutations in U38 DNA polymerase or in U69 phosphotransferase gene have demonstrated antiviral resistance to ganciclovir.[58] Mutations in the U38 gene (P462S and A565V) confer resistance to ganciclovir only,[91] whereas an R798I amino acid change confers resistance to both ganciclovir and cidofovir.[92] Treatment with ganciclovir has a relatively high success rate (Table 5) although cases of ganciclovir-resistant HHV-6 disease in liver transplant patients have been reported.[40]

6.2 | Cidofovir

Cidofovir has been successfully used to treat clinical HHV-6 infections (Table 5). HHV-6 strains with a mutation (R798I) in the U38 DNA polymerase gene have demonstrated antiviral resistance to cidofovir and ganciclovir.[58,92] Thus, if cidofovir resistance is suspected, foscarnet should be the next line of therapy. Nephrotoxicity is the most common serious adverse effect of cidofovir,[93] which should be used with caution when concomitantly administrated with potentially nephrotoxic agents (including but not limited to foscarnet, antibiotics and NSAIDs).

6.3 | Foscarnet (PFA or phosphonoformate)

Foscarnet is considered the most selective in vitro inhibitor of HHV-6 among the three drugs currently used to clinically treat active HHV-6 infections.[94] Foscarnet selectively inhibits pyrophosphate binding on viral DNA polymerases. Mutations in U38 DNA polymerase (T435R, H507Y, C525S, located in the deltaC conserved domain and F292S) provides HHV-6 antiviral resistance to foscarnet,[95] which are distinct from the U38 mutations that confer resistance to cidofovir and ganciclovir.[58,91,92] Foscarnet is the preferential treatment option for HHV-6 encephalitis in patients with anaemia, as administration of ganciclovir poses an additionally risk of dose-limiting haematological toxicity. Both drugs are able to penetrate the blood-brain barrier.[84] Risks associated with foscarnet include complications from catheter-related deep vein thrombosis and infection.[84] Nephrotoxicity is the most common serious adverse effect of foscarnet, affecting 30% of patients, and is caused by deposition of foscarnet crystals in the glomerular capillary lumen.[93] Foscarnet can also chelate bivalent metal ions and may lead to reductions in ionized calcium. Other electrolyte disturbances are hypokalaemia, hypomagnesaemia and hypophosphatasaemia, which can manifest as paresthesias, cardiac dysrhythmias and neurological symptoms, including seizures.[93] Unlike cidofovir, foscarnet cannot be administered in a peripheral vein.[94]

6.4 | Prophylaxis

There are no standard guidelines that recommend prophylaxis against HHV-6 in liver transplant patients since the prophylaxis for CMV also covers HHV-6 (Table 3). Investigators who conducted a study of 34 paediatric liver transplant patients using routine antiviral prophylaxis for CMV reported a low frequency of HHV-6 DNA detection in whole blood (16%) post-transplant and an even lower frequency of plasma viraemia (2.6%), and hypothesized that these low rates may have been in part because of the ganciclovir treatment.[29] A study of 129 adult liver transplant patients found that monitoring for HHV-6 in liver transplant patients did not significantly alter the primary outcome. CMV prophylaxis (valganciclovir) was administered to 39% of the non-monitored group and 30% of the monitored group, and only one out of 23 episodes (4.3%) of HHV-6 viraemia occurred in patients receiving prophylaxis (Table 3).[14] Another study of 23 paediatric liver transplant patients who received ganciclovir/valganciclovir prophylaxis, reported similar results, detecting HHV-6 in just one patient (4.3%).[96]

6.5 | Viral monitoring and preemptive therapy

Monitoring for HHV-6 viraemia is not routinely recommended. A Japanese study monitoring 34 liver transplant recipients (17 adult, 17 paediatric) not given antiviral prophylaxis detected HHV-6 in 20.6% of patients and viraemia occurred briefly without clinical symptoms.[63] A recent study of 129 liver transplant recipients compared the outcomes of 64 patients monitored for HHV-6 viraemia with the outcomes of 65 patients not monitored for HHV-6 viraemia.[14] There were no differences in cumulative incidence of primary outcome between the monitored and non-monitored groups at 1-year or 5-year post-transplant. However, a trend towards a lower incidence of graft rejection at year 1 post-transplant (P=.091) and a significantly lower cumulative incidence of biopsy proven acute graft rejection in the monitoring group (P=.026) were observed. This study reported only 1 of 23 episodes of HHV-6 viraemia in patients on valganciclovir prophylaxis.[14]

7 | SUMMARY

Although acute clinical disease attributed to HHV-6 after liver transplantation is rare, HHV-6 infections may impact the liver transplant patient. This review indicates that HHV-6 reactivation in liver transplant recipients is associated with significant increases in graft failure, mortality, hepatitis C progression and fibrosis and CMV disease.[97–100] Risk factors include steroid usage, HHV-6 seronegativity, hepatitis B or C and immunosuppressive agents such alemtuzumab. HHV-6 viraemia may occur more frequently in paediatric patients than in adults, owing to the occurrence of HHV-6 primary infection in the paediatric

population. HHV-6 may be an underappreciated cause of acute liver failure of unknown aetiology and pretransplant HHV-6 infection in patients with ALF may be a risk factor for HHV-6 infection of the liver graft post-transplant. Elevated HHV-6 DNA load in biopsy samples is associated with decreased graft survival and mortality. Although acute systemic HHV-6 infection is currently diagnosed by quantifying viral DNA in plasma or blood, HHV-6 infection can persist in lung, liver, heart and brain tissues. In these cases, DNA is undetectable in the plasma so biopsy remains the gold standard for diagnosis of end-organ disease. HHV-6 reactivation in the graft cannot be ruled out in the absence of a biopsy. HHV-6 infections in liver transplant patients can be treated successfully with CMV antivirals ganciclovir, cidofovir or foscarnet. Ganciclovir prophylaxis appears to add protection against HHV-6 as well as CMV.

Inherited chromosomally integrated HHV-6 complicates interpretation of HHV-6 positive samples as the inherited virus can activate from its integrated state during immunosuppression.[19] Further study is required to determine if ciHHV-6+ organs should be monitored for reactivation or given antiviral prophylaxis.[83,84]

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CONFLICTS OF INTEREST

None.

REFERENCES

1. Ablashi D, Agut H, Alvarez-Lafuente R, et al. Classification of HHV-6A and HHV-6B as distinct viruses. *Arch Virol*. 2014;159:863-870.
2. DeBolle L, Naesens L, Clercq ED. Update on human herpesvirus 6 biology, clinical features, and therapy. *Clin Microbiol Rev*. 2005;18:217-245.
3. Revest M, Camus C, D'Halluin P-N, et al. Fatal human herpes virus 6 primary infection after liver transplantation. *Transplantation*. 2007;83:1404-1405.
4. Zerr DM, Meier AS, Selke SS, et al. A population-based study of primary human herpesvirus 6 infection. *New Eng J Med*. 2005;352:768-776.
5. Salvaggio MR. Human herpesvirus 6 infection clinical presentation. 2015, http://emedicine.medscape.com/article/219019-clinical. Accessed February 20, 2016.
6. Cermelli C, Concari M, Carubbi F, et al. Growth of human herpesvirus 6 in HEPG2 cells. *Virus Res*. 1996;45:75-85.
7. Inagi R, Guntapong R, Nakao M, et al. Human herpesvirus 6 induces IL-8 gene expression in human hepatoma cell line, Hep G2. *J Med Virol*. 1996;49:34-40.
8. Ohashi M, Sugata K, Ihira M, et al. Human herpesvirus 6 infection in adult living related liver transplant recipients. *Liver Transpl*. 2008;14:100-109.
9. Leveque N, Boulagnon C, Brasselet C, et al. A fatal case of human herpesvirus 6 chronic myocarditis in an immunocompetent adult. *J Clin Virol*. 2011;52:142-145.
10. DeSimone M, Muccio CF, Megna AS, Esposito G. Human herpes virus 6 encephalitis in immunocompetent patient: An unusual neuroradiological presentation. *Clin Neurol Neurosurg*. 2013;115:2219-2222.
11. Cacheux W, Carbonell N, Rosmorduc O, et al. HHV-6-related acute liver failure in two immunocompetent adults: Favourable outcome after liver transplantation and/or ganciclovir therapy. *J Int Med*. 2005;258;573-578.
12. Fujita M, Takahashi A, Imaizumi H, et al. Drug-induced liver injury with HHV-6 reactivation. *Intern Med*. 2015;54:1219-1222.
13. Ozaki Y, Tajiri H, Tanaka-Taya K, et al. Frequent detection of the human herpesvirus 6-specific genomes in the livers of children with various liver diseases. *J Clin Microbiol*. 2001;39:2173-2177.
14. Fernández-Ruiz M, Kumar D, Husain S, et al. Utility of a monitoring strategy for human herpesviruses 6 and 7 viremia after liver transplantation: A randomized clinical trial. *Transplantation*. 2015;99:106-113.
15. Feldstein AE, Razonable RR, Boyce TG, et al. Prevalence and clinical significance of human herpesviruses 6 and 7 active infection in pediatric liver transplant patients. *Pediatr Transplant*. 2003;7:125-129.
16. Lautenschlager I, Linnavuori K, Hockerstedt K. Human herpesvirus-6 antigenemia after liver transplantation. *Transplantation*. 2000;69:2561-2566.
17. Schmidt CA, Wilbron F, Weiss K, et al. A prospective study of human herpesvirus type 6 detected by polymerase chain reaction after liver transplantation. *Transplantation*. 1996;61:662-664.
18. Kaufer BB, Flamand L. Chromosomally integrated HHV-6: Impact on virus, cell and organismal biology. *Curr Opin Virol*. 2014;9:111-118.
19. Endo A, Watanabe K, Ohye T, et al. Molecular and virological evidence of viral activation from chromosomally integrated human herpesvirus 6A in a patient with X-linked severe combined immunodeficiency. *Clin Infect Dis*. 2014;59:545-548.
20. Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6: Questions and answers. *Rev Med Virol*. 2012;22:144-155.
21. Lee S-O, Brown RA, Razonable RR. Clinical significance of pretransplant chromosomally integrated human herpesvirus-6 in liver transplant recipients. *Transplantation*. 2011;92:224-229.
22. Arbuckle JH, Medveczky MM, Luka J, et al. The latent human herpesvirus-6A genome specifically integrates in telomeres of human chromosomes in vivo and in vitro. *Proc Natl Acad Sci USA*. 2010;197:5563-5568.
23. Costa FA, Soki MN, Andrade PD, et al. Simultaneous monitoring of CMV and human herpesvirus 6 infections and diseases in liver transplant patients: One-year follow-up. *Clinics*. 2011;66:949-953.
24. Yoshikawa T, Ihira M, Suzuki K, et al. Human herpesvirus 6 infection after living related liver transplantation. *J Med Virol*. 2000;62:52-59.
25. Dohna-Schwake C, Fiedler M, Gierenz N, et al. Primary HHV 6 infection after liver transplantation with acute graft rejection and multi-organ failure: Successful treatment with a 2.5-fold dose of cidofovir and reduction of immunosuppression. *Pediatr Transplant*. 2011;15:E126-E129.
26. Chevret L, Boutolleau D, Halimi-Idri N, et al. Human herpesvirus-6 Infection: A prospective study evaluating HHV-6 DNA levels in liver from children with acute liver failure. *J Med Virol*. 2008;80:1051-1057.
27. Singh N, Carrigan DR, Gayowski T, Marino IR. Human herpesvirus-6 infection in liver transplant recipients: Documentation of pathogenicity. *Transplantation*. 1997;64:674-678.
28. Humar A, Kumar D, Caliendo AM, et al. Clinical impact of human herpesvirus 6 after liver transplantation. *Transplantation*. 2002;73:599-604.
29. Fawaz TA, Ng V, Richardson SE, Barton M, Allen U. Clinical consequences of human herpesvirus-6 DNAemia in peripheral blood in pediatric liver transplant recipients. *Pediatr Transplant*. 2014;18:47-51.
30. Potenza L, Luppi M, Barozzi P, et al. HHV-6A in syncytial giant-cell hepatitis. *New Eng J Med*. 2008;359:593-602.
31. Buyse S, Roque-Afonso A-M, Vaghefi P, et al. Acute hepatitis with periportal confluent necrosis associated with human

herpesvirus 6 infection in liver transplant patients. *Am J Clin Pathol*. 2013;140:403-409.
32. Lautenschlager I, Hockerstedt K, Linnavuori K, Taskinen E. Human herpesvirus-6 infection after liver transplantation. *Clin Infect Dis*. 1998;26:702-707.
33. Ogata M. Human herpesvirus-6 encephalitis in allogeneic hematopoietic stem cell transplantation. *Brain Nerve*. 2015;67:919-930.
34. Hill JA, Koo S, Guzman Suarez BB, et al. Cord-blood hematopoietic stem cell transplant confers an increased risk for human herpesvirus-6-associated acute limbic encephalitis: A cohort analysis. *Biol Blood Marrow Transplant*. 2012;18:1638-1648.
35. Scheurer ME, Pritchett JC, Amirian ES, Zemke NR, Lusso P, Ljungman P. HHV-6 encephalitis in umbilical cord blood transplantation: A systematic review and meta-analysis. *Bone Marrow Transplant*. 2013;48:574-580.
36. Magalhães GS, Guardia AC, Sampaio AM, Boin IFSF, Stucchi RSB. HHV-6: Clinical and laboratory investigations and correlations with encephalitis in liver transplant recipients. *Transpl Proc*. 2013;45:1997-1999.
37. Vinnard C, Barton T, Jerud E, Blumberg E. A report of human herpesvirus 6–associated encephalitis in a solid organ transplant recipient and a review of previously published cases. *Liver Transpl*. 2009;15:1242-1246.
38. Montejo M, Fernandez JR, Testillano M, et al. Encephalitis caused by human herpesvirus-6 in a liver transplant recipient. *Eur Neurol*. 2002;48:234-235.
39. Paterson DL, Singh N, Gayowski T, Carrigan DR, Marino IR. Encephalopathy associated with human herpesvirus 6 in a liver transplant recipient. *Liver Transpl Surg*. 1999;5:454-455.
40. Baldwin K. Ganciclovir-resistant human herpesvirus-6 encephalitis in a liver transplant patient- a case report. *J Neurovirol*. 2011;17:193-195.
41. Revest M, Minjolle S, Veyer D, Lagathu GL, Michelet C, Colimon R. Detection of HHV-6 in over a thousand samples: New types of infection revealed by an analysis of positive results. *J Clin Virol*. 2011;51:20-24.
42. Halme L, Arola J,¨ckerstedt KH, Lautenschlager I. Human herpesvirus 6 infection of the gastroduodenal mucosa. *Clin Infect Dis*. 2008;46:434-439.
43. Miura H, Kawamura Y, Ozeki E, Ihira M, Ohashi M, Yoshikawa T. Pathogenesis of severe neutropenia in patients with primary human herpesvirus 6b infection. *Pediatr Infect Dis J*. 2015;34:1003-1007.
44. Razonable RR, Lautenschlager I. Impact of human herpes virus 6 in liver transplantation. *World J Hepatol*. 2010;2:345-353.
45. Dagna L, Pritchett JC, Lusso P. Immunomodulation and immunosuppression by human herpesvirus 6A and 6B. *Future Virol*. 2013;8:273-287.
46. Harma M, Hockerstedt K, Lyytikainen O, Lautenschlager I. HHV-6 and HHV-7 antigenemia related to CMV infection after liver transplantation. *J Med Virol*. 2006;78:800-805.
47. Sampaio AM, Guardia AC, Milan A, et al. Co-infection and clinical impact of human herpesvirus 5 and 6 in liver transplantation. *Transpl Proc*. 2012;44:2455-2458.
48. DesJardin JA, Cho E, Supran S, Gibbons L, Werner BG, Snydman DR. Association of human herpesvirus 6 reactivation with severe cytomegalovirus- associated disease in orthotopic liver transplant recipients. *Clin Infect Dis*. 2001;33:1358-1362.
49. Mendez JC, Dockrell DH, Espy MJ, et al. Human b-herpesvirus interactions in solid organ transplant recipients. *J Infect Dis*. 2001;183:179-184.
50. Razonable RR, Burak KW, Hv Cruijsen, et al. The pathogenesis of hepatitis C virus is influenced by cytomegalovirus. *Clin Infect Dis*. 2002;35:974-981.
51. Humar A, Washburn K, Freeman R, et al. An assessment of interactions between hepatitis C virus and herpesvirus reactivation in liver transplant recipients using molecular surveillance. *Liver Transpl*. 2007;13:1422-1427.
52. Guardia AC, Stucchi RSB, Sampaio AM, et al. Human herpesvirus 6 in donor biopsies associated with the incidence of clinical cytomegalovirus disease and hepatitis C virus recurrence. *Int J Infect Dis*. 2012;16:e124-e129.
53. Flamand L, Komaroff AL, Arbuckle JH, Medveczky PG, Ablashi DV. Review, Part 1: Human herpesvirus-6 – basic biology, diagnostic testing, and antiviral efficacy. *J Med Virol*. 2010;82:1560-1568.
54. Singh N, Bentlejewski C, Carrigan DR, Gayowski T, Knox KK, Zeevi A. Persistent lack of human herpesvirus-6 specific T-helper cell response in liver transplant recipients. *Transpl Infect Dis*. 2002;4:59-63.
55. Rogers J, Rohal S, Carrigan D, et al. Human herpesvirus-6 in liver transplant recipients: Role in pathogenesis of fungal infections, neurologic complications, and outcome. *Transplantation*. 2000;69:2566-2573.
56. Lautenschlager I, Hockerstedt K, Linnavuori K, Taskinen E. Human herpesvirus 6 infection increases adhesion molecule expression in liver allografts. *Transpl Proc*. 1999;31:479-480.
57. Lautenschlager I, Harma M,¨Ckerstedt KH, Linnavuori K, Loginov R, Taskinen E. Human herpesvirus-6 infection is associated with adhesion molecule induction and lymphocyte infiltration in liver allografts. *J Hepatol*. 2002;37:648-654.
58. Massih RCA, Razonable RR. Human herpesvirus 6 infections after liver transplantation. *World J Gastroenterol*. 2009;15:2561-2569.
59. Pischke S, Gösling J, Engelmann I, et al. High intrahepatic HHV-6 virus loads but neither CMV nor EBV are associated with decreased graft survival after diagnosis of graft hepatitis. *J Hepatol*. 2012;56:1063-1069.
60. Guardia AC, Stucchi RSB, Milan A, Costa SClB, Boin IdFtSF. Human herpesvirus-6 and cytomegalovirus DNA in liver donor biopsies and their correlation with HLA matches and acute cellular rejection. *Braz J Infectious Dis*. 2014;18:220-224.
61. Cervera C, Marcos MA, Linares L, et al. A Prospective Survey of Human Herpesvirus-6 Primary Infection in Solid Organ Transplant Recipients. *Transplantation*. 2006;82:979-982.
62. Mysore KR, Himes RW, Munoz FM. HHV-6 infection in pediatric liver transplant recipients at texas children's hospital. In: *Oral Presentation at the 9th International Conference on HHV-6 & 7*, Boston, MA, October 2015.
63. Ono Y, Ito Y, Kaneko K, et al. simultaneous monitoring by real-time polymerase chain reaction of epstein-barr virus, human cytomegalovirus, and human herpesvirus- 6 in juvenile and adult liver transplant recipients. *Transpl Proc*. 2008;40:3578-3582.
64. Black JB, Sanderlin KC, Goldsmith CS, Gary HE, Lopez C, Pellett PE. Growth properties of human herpesvirus-6 strain Z29. *J Virol Methods*. 1989;26:133-145.
65. Ishida T, Kano Y, Mizukawa Y, Shiohara T. The dynamics of herpesvirus reactivations during and after severe drug eruptions: Their relation to the clinical phenotype and therapeutic outcome. *Allergy*. 2014;69:799-805.
66. Harma M, Hockerstedt K, Lautenschlager I. Human herpesvirus-6 and acute liver failure. *Transplantation*. 2003;76:536-539.
67. Harma M, Hockerstedt K, Krogerus L, Lautenschlager I. Pretransplant human herpesvirus 6 infection of patients with acute liver failure is a risk factor for posttransplant human herpesvirus 6 infection of the liver. *Transplantation*. 2006;81:367-372.
68. Komaroff AL, Phan T, Flamand L, Pellett PE. Summary of the 9th International Conference on Human herpesviruses 6 and 7 (HHV-6A, HHV-6B and HHV-7). *J Med Virol*. 2016;88:2038-2043.
69. Flamand L, Gravel A, Boutolleau D, et al. Multicenter comparison of PCR assays for detection of human herpesvirus 6 DNA in serum. *J Clin Microbiol*. 2008;46:2700-2706.
70. Govind S, Almond N, Minor P, Morris C. Towards establishing the 1st WHO international standards for human herpesviruses 6A and 6B, for NAT-based assays. In: *Oral presentation at the 9th International Conference on HHV-6 & 7*, Boston, MA, October 2015.

71. de Pagter PJ, Schuurman R, de Vos NM, Mackay W, van Loon AM. Multicenter external quality assessment of molecular methods for detection of human herpesvirus 6. *J Clin Microbiol*. 2010;48:2536-2540.
72. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev*. 2015;28:313-335.
73. Maharaj B, Bhoora IG. Complications associated with percutaneous needle biopsy of the liver when one, two or three specimens are taken. *Postgrad Med J*. 1992;68:964-967.
74. Seo S, Renaud C, Kuypers JM, et al. Idiopathic pneumonia syndrome after hematopoietic cell transplantation: Evidence of occult infectious etiologies. *Blood*. 2015;125:3789-3797.
75. Siddon A, Lozovatsky L, Mohamed A, Hudnall SD. Human herpesvirus 6 positive Reed-Sternberg cells in nodular sclerosis Hodgkin lymphoma. *Br J Haematol*. 2012;158:635-643.
76. Ishikawa K, Hasegawa K, Naritomi T, et al. Prevalence of herpesviridae and hepatitis virus sequences in the livers of patients with fulminant hepatitis of unknown etiology in Japan. *J Gastroenterol*. 2002;37:523-530.
77. Tajiri H, Tanaka-Taya K, Ozaki Y, Okada S, Mushiake S, Yamanishi K. Chronic hepatitis in an infant, in association with human herpesvirus-6 infection. *J Pediatr*. 1997;131:473-475.
78. Loginov R, Karlsson T, Hockerstedt K, Ablashi D, Lautenschlager I. Quantitative HHV-6B antigenemia test for the monitoring of transplant patients. *Eur J Clin Microbiol Infect Dis*. 2010;29:881-886.
79. Yoshikawa T, Ihira M, Suzuki K, et al. Primary human herpesvirus 6 infection in liver transplant recipients. *J Pediat*. 2001;138:921-925.
80. Gautheret-Dejean A, Bonnafous P, Agut H. Diagnosis and practice of virological monitoring of infections by the human herpesviruses 6A and 6B. *Ann Biol Clin (Paris)*. 2016;74:156-167.
81. Sedlak RH, Coo L, Huang M-L, et al. Identification of chromosomally integrated human herpesvirus 6 by droplet digital PCR. *Clin Chem*. 2014;60:756-772.
82. Potenza L, Barozzi P, Masetti M, et al. Prevalence of human herpesvirus-6 chromosomal integration (CIHHV-6) in Italian solid organ and allogeneic stem cell transplant patients. *Am J Transplant*. 2009;9:1690-1697.
83. Flamand L. Pathogenesis from the reactivation of chromosomally integrated human herpesvirus type 6: Facts rather than fiction. *Clin Infect Dis*. 2014;59:549-551.
84. Lautenschlager I, Razonable RR. HHV-6A and HHV-6B in Solid Organ Transplantation. In: Flamand L, Lautenschlager I, Krueger G, Ablashi D, eds. *Human Herpesviruses HHV-6A, HHV-6B & HHV-7: Diagnosis and Clinical Management*, 3rd edn. Oxford, UK: Elsevier; 2014:201-216.
85. Kuhl U, Lassner D, Wallaschek N, et al. Chromosomally integrated human herpesvirus 6 in heart failure: Prevalence and treatment. *Eur J Heart Fail*. 2015;17:9-19.
86. Montoya JG, Neely MN, Gupta S, et al. Antiviral therapy of two patients with chromosomally-integrated human herpesvirus-6A presenting with cognitive dysfunction. *J Clin Virol*. 2012;55:40-45.
87. Pantry SN, Medveczky MM, Arbuckle JH, et al. Persistent human herpesvirus-6 infection in patients with an inherited form of the virus. *J Med Virol*. 2013;85:1940-1946.
88. Lee SO, Brown RA, Razonable RR. Chromosomally integrated human herpesvirus-6 in transplant recipients. *Transpl Infect Dis*. 2012;14:346-354.
89. Manichanh C, Grenot P, Gautheret-Dejean A, Debré P, Huraux JM, Agut H. Susceptibility of human herpesvirus 6 to antiviral compounds by flow cytometry analysis. *Cytometry*. 2000;40:135-140.
90. Hasegawa T, Kimura T, Sasaki T, et al. Sequential measurement of human herpesvirus 6 DNA with polymerase chain reaction method in pediatric living-related liver transplantation. *Clin Transplant*. 2001;15:208-213.
91. Isegawa Y, Hara J, Amo K, et al. Human herpesvirus 6 ganciclovir-resistant strain with amino acid substitutions associated with the death of an allogeneic stem cell transplant recipient. *J Clin Virol*. 2009;44:15-19.
92. Bonnafous P, Boutolleau D, Naesens L, Deback C, Gautheret-Dejean A, Agut H. Characterization of a cidofovir-resistant HHV-6 mutant obtained by in vitro selection. *Antiviral Res*. 2008;77:237-240.
93. Razonable RR. Antiviral drugs for viruses other than human immunodeficiency virus. *Mayo Clin Proc*. 2011;86:1009-1026.
94. Pritchett JC, Naesens L, Montoya J. Treating HHV-6 Infections. In: Flamand L, Lautenschlager I, Krueger G, Ablashi D, eds. *Human Herpesviruses HHV-6A, HHV-6B & HHV-7: Diagnosis and Clinical Management*, 3rd edn. Oxford, UK: Elsevier; 2014:311-320.
95. Bonnafous P, Naesens L, Petrella S, et al. Different mutations in the HHV-6 DNA polymerase gene accounting for resistance to foscarnet. *Antivir Ther*. 2007;12:877-888.
96. Kourí V, Correa C, Martínez PA, et al. Prospective, comprehensive, and effective viral monitoring in Cuban children undergoing solid organ transplantation. *SpringerPlus*. 2014;3:247.
97. Singh N, Husain S, Carrigan DR, et al. Impact of human herpesvirus-6 on the frequency and severity of recurrent hepatitis C virus hepatitis in liver transplant recipients. *Clin Transplant*. 2002;16:92-96.
98. Humar A, Kumar D, Rabou J, et al. Interactions between cytomegalovirus, human herpesvirus-6, and the recurrence of hepatitis C after liver transplantation. *Am J Transplant*. 2002;2:461-466.
99. Humar A, Malkan G, Moussa G, Greig P, Levy G, Mazzulli T. Human herpesvirus–6 Is associated with cytomegalovirus reactivation in liver transplant recipients. *J Infect Dis*. 2000;181:1450-1453.
100. Te HS, Drobeniuc J, Kamili S, Dong C, Hart J, Sharapov UM. Hepatitis E virus infection in a liver transplant recipient in the United States: A case report. *Transpl Proc*. 2013;45:810-813.

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